$300.00 120
20/Appeal Brief (3)
Bet 7-14-97

Docket No. 4733

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS & INTERFERENCES

Appellants:	Eugene P. GOLDBERG, ET AL
Serial No.:	08/141,017
Filed:	October 26, 1993
For:	METHOD OF AND COMPOSITION FOR PREVENTING TISSUE DAMAGE
Art Unit:	1502
Examiner:	Edward J. Webman

BRIEF ON APPEAL

Hon. Commissioner of Patents & Trademarks
Washington, D.C. 20231

Sir:

The attached Brief on Appeal is submitted in support of the appeal of the Office Action mailed January 8, 1997, wherein the Examiner finally rejected claims 1, 2 and 5-7.

The Appeal Fee in the amount of $300.00 is appended hereto.

To the extent necessary, appellants petition for an extension of time under 37 CFR §1.136. Please charge any additional fees due to Deposit Account No. 11-0610 (Docket 4733).

Respectfully submitted,

KERKAM, STOWELL,
KONDRACKI & CLARKE, P.C.

Dennis P. Clarke
Registration No. 22,549

DPC:lef

Two Skyline Place, Suite 600
5203 Leesburg Pike
Falls Church, VA 22041-3401
Telephone: (703) 998-3302

TABLE OF CONTENTS

TABLE OF AUTHORITIES

REAL PARTY IN INTEREST

The real party in interest herein is the University of Florida Research Foundation, Inc., as evidenced by an Assignment recorded in the U.S. Patent and Trademark Office as of May 23, 1994, on Reel 6993 at Frame 0676.

RELATED APPEALS AND INTERFERENCES

The following pending appeals, all in the name of Eugene P. Goldberg et al, are related to the instant appeal:

1. Serial No. 07/750,840 filed August 29, 1991
2. Serial No. 08/202,647 filed February 28, 1994
3. Serial No. 08/210,454 filed March 21, 1994
4. Serial No. 08/362,890 filed December 23, 1994
5. Serial No. 08/485,832 filed June 7, 1995

STATUS OF CLAIMS

This is an appeal from the final rejection of claims 1, 2 and 5-7. Claims 3 and 4 are withdrawn from further consideration as being for a non-elected invention. Original claims 8-14 have been cancelled. No other claims remain in the application.

STATUS OF AMENDMENTS

No amendments have been filed subsequent to the issuance of the final rejection.

SUMMARY OF INVENTION

The present invention relates to a method for preventing tissue damage during surgery. Tissue and organ surfaces involved in surgery are susceptible to tissue damage and adhesions as a result of the manipulative trauma of the surfaces during surgery, as well as other causes such as drying and ischemic trauma. In addition to the formation of post-operative adhesions, tissue trauma during surgery can lead to a variety of potentially serious complications during and following surgical procedures. These include excessive blood vessel damage with increased bleeding during surgery and the greater risk of post-operative hemorrhage; the enhancement of post-operative inflammation with prolongation of healing; compromised wound healing with excessive scar tissue; damage to organs and tissues which result in impaired organ function; blood vessel damage which reduces blood supply with concomitant partial ischemia of muscle tissues and organs; and increased susceptibility to acute and chronic infections due to the preferential adherence and growth of pathogens on damaged tissue sites.

The method of the invention greatly reduces the above-noted instances of tissue damage and aids in the protection of tissue during surgery. The method of the invention comprises providing the surfaces involved in surgery with a wet coating of an aqueous solution of a hydrophilic, polymeric material prior to manipulation of the tissue. The crux of the invention

resides in the particular polymeric material employed and its concentration in the aqueous solution. It is also critical to the invention that the surfaces to be involved in surgery must be coated prior to any manipulation of the tissue. The polymeric material must be a water-soluble, biocompatible, pharmaceutically acceptable polypeptide, polysaccharide, synthetic polymer, salt, complex or mixture thereof having certain well defined molecular weights. The polymeric material must also be employed within well defined concentration limits in the aqueous solutions applied to the surfaces involved in surgery. It has been found that operation outside of these critical molecular weight and concentration limits will not provide the unobvious and unexpected results achieved by the method of the present invention. It has also been found that utilizing the compositions of the invention after surgery has been initiated will not give rise to these advantageous results.

ISSUES ON APPEAL

Claims 1, 2 and 5-7 stand finally rejected under 35 USC §103 as unpatentable over Balazs.

The issue thus presented for appeal is whether the Examiner has made out a prima facie case of obviousness of the subject matter claimed in claims 1, 2 and 5-7 based upon the reference to Balazs.

GROUPING OF CLAIMS

As provided in 37 CFR §1.192(c)(5), appellants herein concede that all of the rejected claims stand or fall together.

ARGUMENTS

As noted above, there are three critical elements in the claimed method:

(1) The polymeric material must have a molecular weight above 50,000 D (unless the polymeric material is hyaluronic acid, in which case its molecular weight may not be greater than 1,500,000);

(2) The concentration of the polymeric material in the aqueous solution must be in the range of from 0.01% to 15%; and

(3) The solution must be applied to the surfaces involved in surgery prior to manipulation of the tissue during surgery.

As will be shown below, Balazs does not disclose or suggest that two of these limitations are critical, much less that all three must be adhered to in order to produce the results enabled by the method of the invention.

The Molecular Weight Of The Polymeric Material

The only polymeric material disclosed by Balazs is hyaluronic acid. In the discussion of the prior art at column 1, lines 31-37, Balazs discloses:

> "....[t]he molecular weight of this material is generally within the range of 50,000 to 8,000,000 (although there are reports of HUA having molecular weights as high as 13,000,000) depending on the source, method of isolation and method of determination..."

Balazs characterizes his invention as enabling the "provision of a new, ultrapure HUA (hyaluronic acid) which is non-inflammatory" (column 3, lines 19-21). At column 3, lines 50-53, Balazs states:

> "...the preferred combination according to the invention is a HUA molecular weight of at least about 750,000, preferably at least about 1,200,000..."

At column 4, lines 17-19, Balazs states:

> "...Thus, the principal object of the invention is an isolated fraction of HUA (1) of high molecular weight..."

Balazs further states at column 4, lines 42-47:

> "...In more detail this product according to the invention is a HUA fraction having
>
> (a) an average molecular weight greater than about 750,000, preferably greater than about 1,200,000..."

In column 5, lines 14-35, Balazs discusses in detail his characterization of the criticality of the molecular weight of HUA:

> "...HUA extracted from tissue is polydisperse with respect to molecular weight. The fraction which is the object of this invention is also polydisperse, containing HUA molecules covering a range of molecular weights. The measured molecular weight is thus an average value for the molecules in the collected fraction. The average value of at least about 750,000 is the weight average molecular weight..."

Note also the disclosure in column 11, lines 16-19 of Balazs:

> "...the efficiency of this initial cleaning step allows production of molecular weights significantly higher than the minimum 750,000 noted above..."

At lines 47-50 of column 11, it is noted:

> "...The major objective of stage II is to obtain the highest possible yield of HUA from the tissue without degrading the macromolecule to a lower molecular weight..."

Finally, and most critically, the only specific example in the patent to a hyaluronic solution and how to prepare it is from column 10, line 45 (Stage I) to column 13, line 54 (Stage V). At column 13, line 45, it is stated that the molecular weight is 1,586,000. Coupled with the statements in the patent that only high molecular weights are operable, it would appear that the effective lower limit of molecular weight for any hyaluronic acid disclosed by Balazs is 1,586,000.

It should be apparent that the entire thrust of Balazs with respect to the HUA disclosed therein is to high molecular weight HUA. Indeed, the lowest molecular weight product disclosed is one having a molecular weight of 1,586,000 which is above the maximum for the HUA employed in the presently claimed invention.

The Examiner relies heavily on the disclosure at column 3, lines 50-53 of a HUA with a molecular weight "of at least about 750,000." This somewhat vague reference to a lower limit of molecular weight is a far cry, however, from an actual disclosure thereof. As noted above, the reference taken as a whole points one only to much higher molecular weights. Indeed, the reference does not contain an enabling disclosure of a HUA fraction having a molecular weight below 1,500,000. It is

settled in patent law that, in order for a reference to disclose or suggest something, it must contain a disclosure which enables one skilled in the art to be able to produce it. In re LeGrice, 133 USPQ 365; Phillips v. Ladd, 138 USPQ 421; DuPont v. Ladd, 140 USPQ 297; In re Brown, 141 USPQ 245; In re Foster, 145 USPQ 166; In re Dow, 5 USPQ2d 1529; and In re Grose, 201 USPQ 57. The only enabling disclosure in Balazs is of a process for producing a HUA fraction having a molecular weight above 1,500,000.

There can be no other conclusion, therefore, but that Balazs does not contain any enabling disclosure of a HUA fraction having a molecular weight of below 1,500,000.

Concentration Of Polymeric Material

The claims on appeal specify a concentration of from 0.01% to 15%. Although Balazs discloses concentrations of HUA in aqueous solutions of at least about 0.5%, the reference does not show such concentrations of the lower molecular weight HUA employed in the claimed invention. Thus, the bare disclosure in Balazs of concentrations of at least about 0.5% is meaningless unless it is attached to a description of a HUA fraction having a molecular weight below 1,500,000 which, as shown above, is absent from Balazs.

Note the disclosure in lines 62-66 of column 3 of Balazs:

> "...therapeutically valuable HUA solutions would have to be relatively concentrated, containing high molecular weight HUA with

> pronounced conformational ordering of the macromolecules of the solution..."

Balazs thus seeks to enable the provision of concentrated solutions of HUA having high molecular weights. The present invention is predicated on the discovery that less concentrated[1] solutions of lower molecular weight HUA give rise to the unexpected results produced by the method of the invention.

Application Prior To Surgery

Probably the most critical feature of the claimed invention is the requirement that the solution of polymeric material be coated on the surfaces which will be involved in the surgery prior to any surgical manipulation of the surgically involved tissue.

In the last full paragraph on page 2 of the final Office Action, the Examiner states:

> "...As to the claimed treatment prior to manipulation, Balasz's teaching of protection during surgical administration [column 15, lines 3-9] indicates application prior to manipulation..." [Emphasis added.]

The two terms "during" and "prior" cannot, of course, be equated as synonymous. They have completely different meanings. The term "during" by any definition connotes a process already in progress. The term "prior to" means before the initiation of a process. Webster's Collegiate Dictionary (10th edition, 1994) defines "during" as "at a point in the course of" whereas

---

[1] Note that the appealed claims specify a lower concentration limit of 0.01%.

"prior" is defined as "earlier in time or order." Thus, by their very definitions, these terms are mutually exclusive and one cannot be said to "indicate" the other.

The proof that Balazs does not contemplate application of the solutions prior to initiation of surgery may be found in the reference itself. In Balazs, the solutions are applied or instilled, in every case, only after surgery has begun or has been completed. Note the procedure described in column 8, line 35 to column 9, line 65 of Balazs, wherein it is stated that only after "performing a temporal canthotomy," "extending the skin excision," "exposing the orbital bone," "dissecting skin and tissue free from the bone," "cutting a...piece of bone away," "excising conjunctiva and freeing it from the sclera," "exposing sclera by extending the conjunctival incision laterally," "cauterizing the sclera," and "placing two sutures," that the hyaluronic acid solution is used to "replace withdrawn vitreous." Without question, this disclosure destroys any argument that the hyaluronic acid solution is used prior to surgery. Furthermore, claim 8 of Balazs, which is the claim relating to surgical adhesions, specifically refers to application "during surgery or post-operatively," i.e., application before surgical manipulation is not disclosed.

In the disclosure of Balazs from column 14, line 7 ("Therapeutic Uses of Purified HUA") to column 15, line 40, it is stated, inter alia:

"Therapeutic Uses of Purified HUA

"The sterile HUA product of the invention has therapeutic application in three major areas.

"1. Prevention of fibrous tissue formation

"HUA influences the invasion and activity of cells participating in the acute and chronic inflammatory processes. Thus, the HUA of the invention can be implanted when prevention of excess fibrous tissue formation and consequent development of adhesion and scars are not desirable.

"The present HUA can also be implanted between tendons and their sheaths to minimize adhesion formation after any surgical procedure[2].

(2) Rydell et al, Clinical Orthopaedics, No. 80, October, 1971, pps. 25-32.

"HUA can also be implanted around peripheral nerves and nerve roots after injury or surgery when damage to the connective tissue around the nerve is extensive and excessive scar formation is expected. Implantation of HUA around the healing (regenerating) nerve can protect it from invasion by connective tissue cells.

"Implantation of HUA between mesothelial, pericardial and pleural sheets and on fasciae is indicated when the prevention of adhesion formation between two endothelial or connective tissue membranes is desired.

"Implantation of HUA into the vitreous is indicated after extensive intravitreal surgery (removal of hemorrhages, opacities, etc.) to prevent excessive cellular reaction, and development of fibrous bands and preretinal tissue membranes.

"The aqueous humor may be replaced by HUA after various intraocular surgical procedures that might cause cellular invasion of the anterior chamber, which would endanger the regeneration and function of

> the iris, ciliary body and corneal endothelium.
>
> "2. Separation of tissue surfaces with a biological prosthesis
>
> "HUA can be used to separate tissue surfaces. The elastoviscous quality of HUA and its biological origin provide two advantages. First, it serves as a mechanical protector of the tissue during surgical manipulation and postoperatively; second, it does not cause inflammation, foreign body reaction, or development of a connective tissue capsule.
>
> "The use of HUA as a biological prosthesis in the anterior chamber is indicated after cataract surgery in order to push back prolapsed vitreous and, after resection of the anterior face of the vitreous, to provide separation between the vitreous and cornea.
>
> "This biological prosthesis (HUA) can be used in the anterior chamber after keratoplasty to prevent adhesion formation between the corneal wound and the iris." [Emphasis added.]

The above statements and, in particular, the statement that "[t]he present HUA can also be implanted between tendons and their sheaths to minimize adhesion formation after any surgical procedure" clearly shows that Balazs does not teach the application of hyaluronic acid prior to surgery to prevent adhesion formation, but only during or after surgery.

It should also be noted that two of the applications parent to the present application (Serial Nos. 555,377 and 696,960), which contained claims with this identical limitation as to application prior to surgery, were allowed over Balazs.

It is not seen how this limitation could be viewed oppositely in the present application.

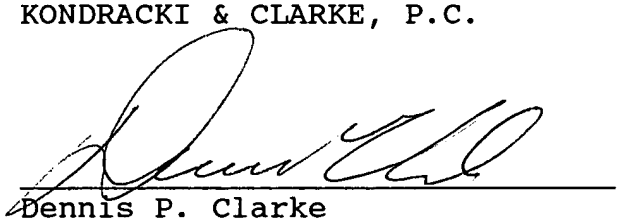
Since Balazs does not disclose or suggest combining the three essential features of the claimed invention, it is respectfully submitted that the Examiner has not made out a prima facie case of obviousness.

CONCLUSION

For the reasons set forth hereinabove, it is respectfully submitted that the Examiner has not made out a prima facie case of obviousness of the claimed invention over Balazs. Accordingly, a reversal of the final rejection and a remand of the case to the Examiner for immediate allowance are respectfully requested.

Respectfully submitted,

KERKAM, STOWELL,
KONDRACKI & CLARKE, P.C.



Dennis P. Clarke
Registration No. 22,549

DPC:lef

Two Skyline Place, Suite 600
5203 Leesburg Pike
Falls Church, VA 22041-3401
Telephone: (703) 998-3302

A P P E N D I X

CLAIMS ON APPEAL

1. A method of protecting tissue and preventing tissue damage in surgery comprising providing surfaces involved in said surgery with a wet coating of a physiologically acceptable aqueous solution of a hydrophilic, polymeric material prior to manipulation of said tissue during said surgery, wherein:

A) said polymeric material is a water-soluble, biocompatible, pharmaceutically acceptable polypeptide, polysaccharide, excluding hyaluronic acid having a molecular weight above about 1,500,000, synthetic polymer, salt, complex or mixture thereof; and

B) said polymeric material has a molecular weight of about 50,000 D or above, and the concentration in said aqueous solution of said polymer is in the range of from about 0.01% to about 15% by weight, said molecular weight and concentration having values such that said aqueous solution is capable of providing wet coatings on said surfaces involved in said surgery.

2. The method of claim 1 wherein said polymeric material is carboxymethylcellulose, PVP, hyaluronic acid, pharmaceutically acceptable salts or complexes thereof or mixtures thereof.

5. The method of claim 2 wherein said polymeric material is hyaluronic acid or a pharmaceutically acceptable salt or complex thereof.

6. The method of claim 1 wherein said surgery is abdominal, peritoneal, pericardial, obstetric, gynecological, neurosurgical, arthroscopic, laparoscopic, endoscopic, orthopedic, plastic, reconstructive, prosthetic, ENT, dental, muscle or tendon.

7. The method of claim 1 wherein said involved surfaces coated with said solution of polymeric material comprise tissue or surgical article surfaces or both.